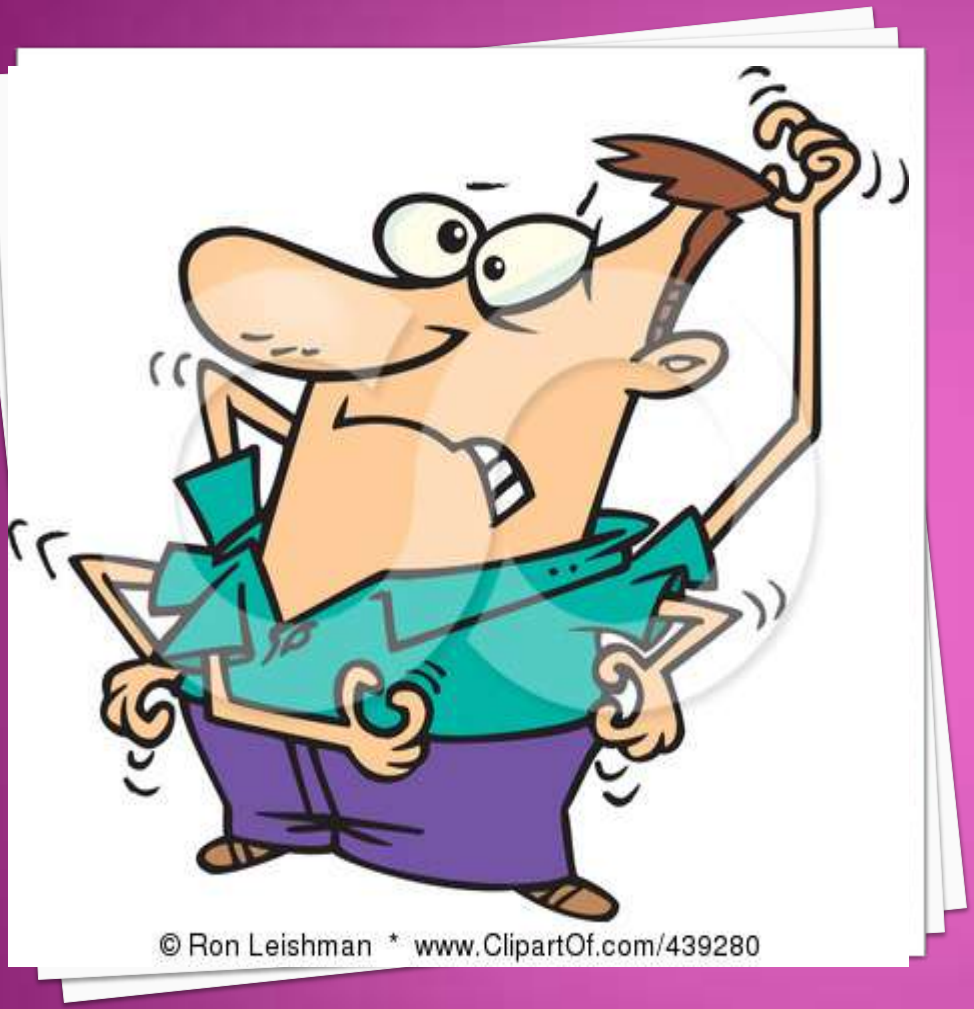


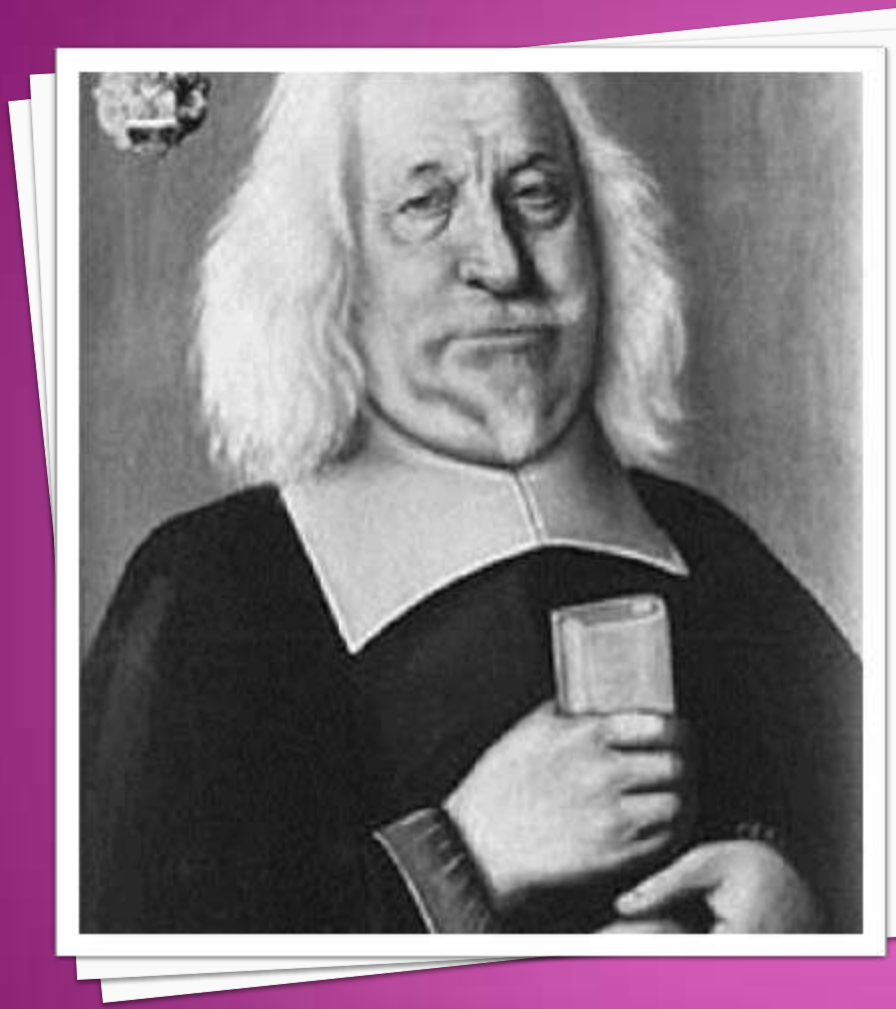
UPDATE IN MANAGEMENT OF CKD ASSOCIATED PRURITS

By

Alaa Sabry, MD

Mansoura University

WHY CKD ASSOCIATED PRURITIS ?



SAMUEL HAFENREFFER 1587-1660) WAS A GERMAN PHYSICIAN, WHO INTRODUCED THE DEFINITION OF PRURITUS.

AJKD

QUIZ PAGE
AUGUST 2014

Pruritus in a Dialysis Patient

CLINICAL PRESENTATION

A 63-year-old man developed pruritus after 12 years of receiving dialysis through a left forearm arteriovenous fistula to treat end-stage renal disease of unknown cause. He experienced generalized chronic itching that was most intense on his upper back and worse during and after dialysis treatments

or psychiatric history. He had a history of allergies (pollen and dust), hypertension, anemia, and hyperparathyroidism. His medications included trandolapril, beta erythropoietin, sevelamer hydrochloride, diphenhydramine, skin moisturizers, liquid powder with menthol, and gabapentin.

Physical examination revealed no stigmata of other diseases. He did not have a rash or other skin lesions, except secondary excoriations on his upper back and mild skin scaling suggestive of xerosis.

Despite standard treatment, the intensity of the patient's pruritus worsened significantly, and he was admitted for further evaluation. Abnormal

LAB. WORK UP

Test	Results	Reference Range
SUN (mg/dL)	69.2	7.56-23.81

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

QUIZ PAGE
AUGUST 2014

Pruritus in a Dialysis Patient

- What does the skin biopsy show, and what is the diagnosis?

scintigraphy parathyroid gland

Note: Conversion factors for units: Calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; SUN in mg/dL to mmol/L, ×0.357.

Abbreviations: IgE, immunoglobulin E; PTH, parathyroid hormone; RBC, red blood cell; SUN, serum urea nitrogen.

UREMIC PRURITIS

Pruritus, derived from the Latin word prurire, which means to itch, is defined as "an unpleasant sensation associated with the desire to scratch"

Frequent concern for hemodialysis patients with the most frustrating and disabling symptoms.

Pruritus is one of the most common cuteanous symptoms associated with ESRD.

M.Metz, et al "Pruritus: an overview of current concepts, *Dermatology, 2011*

Males have a higher prevalence .

High BUN, B2-microglobulin, calcium and phosphate as well as I-PTH

A high prevalence of HLA-B35 .

Pisoni, R.L., *et al. (2006) Nephrology Dialysis Transplantation, 21, 3495-3505*

THE INTERNATIONAL FORUM FOR THE STUDY OF ITCH (IFSI)

In 2007, IFSI proposed a clinically oriented classification scheme consisting of 6 categories :

(1) Dermatological (atopic dermatitis, psoriasis, etc.),

(2) Systemic (kidney dialysis, liver cholestasis, etc.).

(3) Neurological (postherpetic neuralgia, etc.),

(4) Psychogenic (e.g., delusional parasitosis),

(5) Mixed (overlapping and coexistence of several diseases), (6) Others (undetermined origin)

Acta Derm Venereol 2007; 87: 291–294

SPECIAL REPORT

Clinical Classification of Itch: a Position Paper of the International Forum for the Study of Itch

CLINICAL CHARACTERISTICS

Half of patients have generalized itching, and in the other half, pruritus is localized to the back, limbs, chest or head ,face and the acess arm.

Pruritus is intermittent or prolonged over hours and days.

Uremic pruritus is chartictcristically most severe at night and during the hemodialysis; however, some patients experience severe discomfort almost continuously.

In contrast to dermatological pruritus, primary skin lesions are not commonly observed in patients with CKD-aP.

Many patients with chronic renal failure first develop pruritus only after institution of hemodialysis dialysis for more than 3 months.

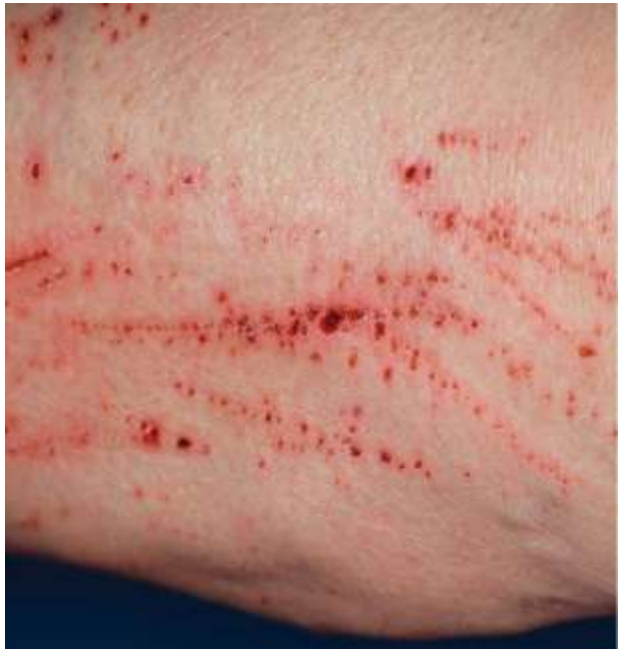
Pisoni RL et al.. Nephrol Dial Transplant 2006

http://www.kidney-international.org
mini review

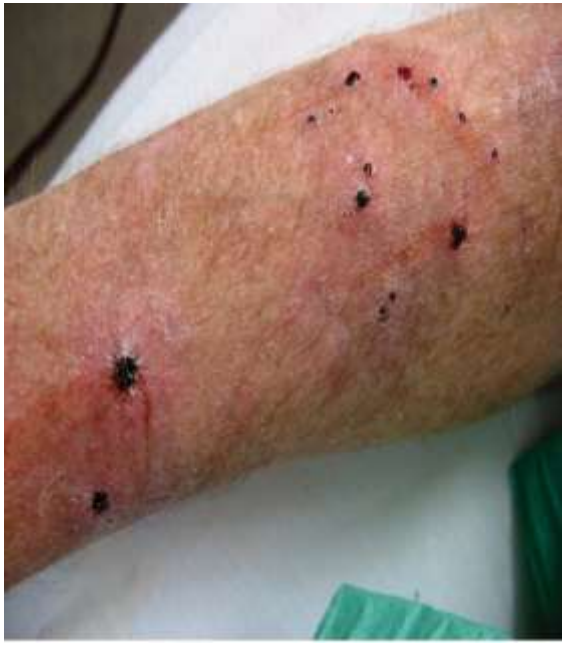
Uremic pruritus

Thomas Mettang[1] and Andreas E. Kremer[2]

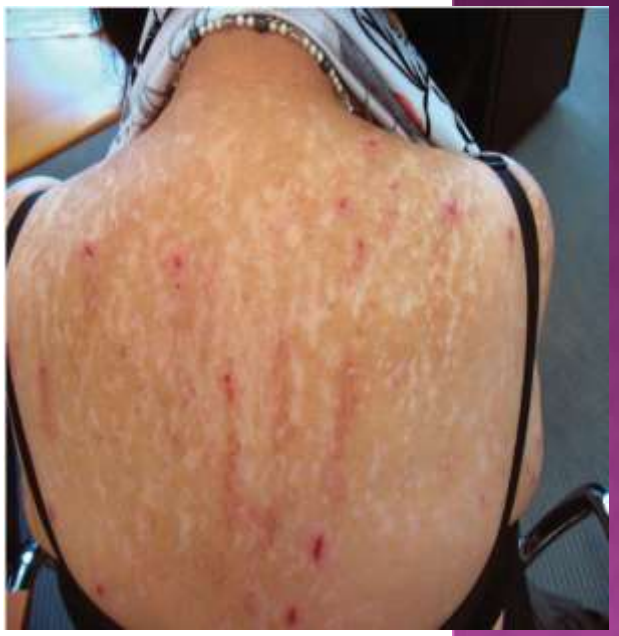
[1]Department of Nephrology, Deutsche Klinik für Diagnostik, Wiesbaden, Germany and [2]Department of Medicine 1, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany



Scratch marks with excoriations at the lower leg.



Typical hyperkeratotic partly excoriated nodules (prurigo nodularis).



Deep scars and prurigo nodules at the shoulders and back.

http://www.kidney-international.org mini review

Uremic pruritus

Thomas Mettang[1] and Andreas E. Kremer[2]

[1]Department of Nephrology, Deutsche Klinik für Diagnostik, Wiesbaden, Germany and [2]Department of Medicine 1, Friedrich-... University of Erlangen-Nuremberg, Erlangen, Germany

Epidemiology

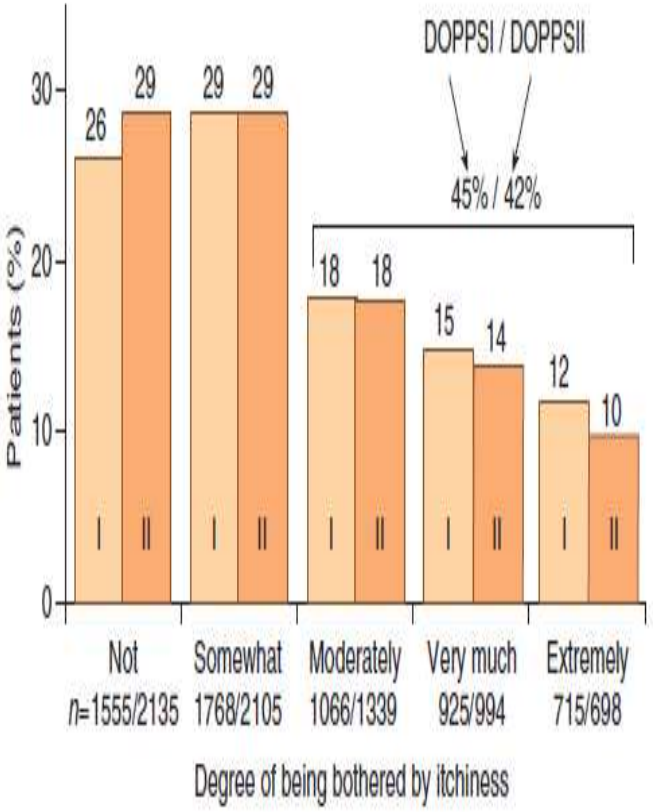
In the early days of dialysis treatment (In 1970s) , CKD-aP was a very common problem afflicting up to 85% of patients

The DOPPS 18,801 HD

Peritoneal dialysis

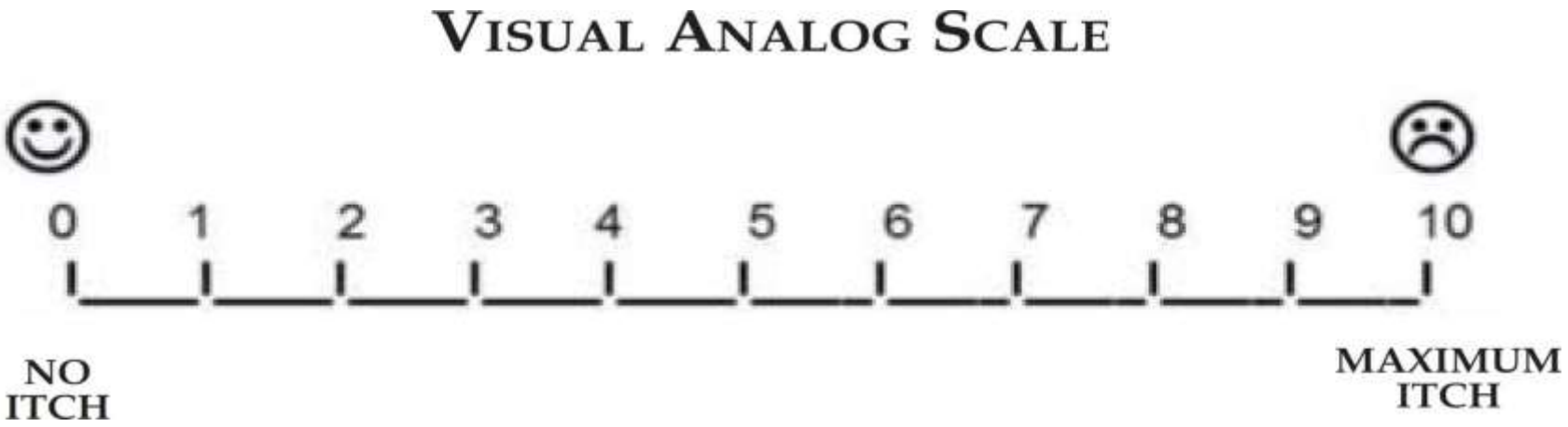
Data on the prevalence in peritoneal dialysis are rather scarce.

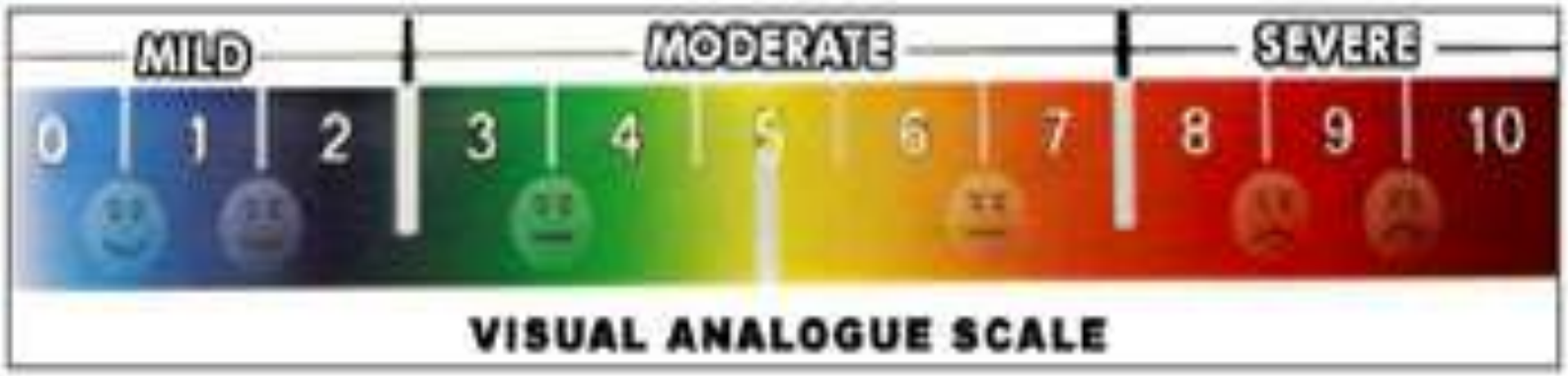
The few reports available, patients undergoing peritoneal dialysis are similarly affected by pruritus as patients on hemodialysis.



DOPPS-data from 1996 to 1999 (I) and 2002 to 2003 (II)

VISUAL ANALOGUE SCALE





QUALITY OF LIFE

Significant associations were found among itching intensity, severity, and (HR-QOL).

Patients who suffer from pruritus also have a lower HR-QOL including sleep disturbances, depression which may lead to poor prognosis.

Narita, I *et al. (2006) Kidney International, 69, 1626-1632.*

Uremic pruritus is associated increased (17%) mortality rate in undergoing HD patients

Pisoni *et al* Nephrol Dial Transplant (2006) 21: 3495–3505*.*

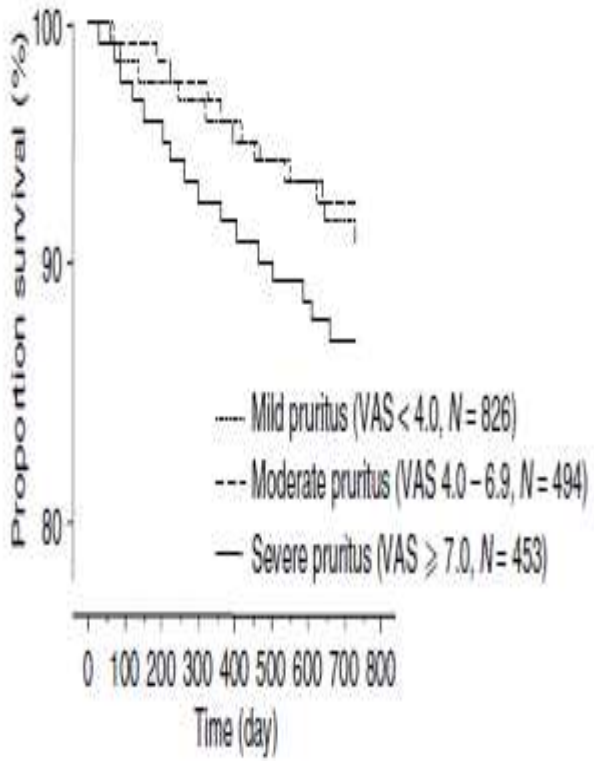


Figure 3 | Kaplan-Meier analysis for the survival of patients. The prognosis of patients with severe uremic pruritus was significantly worse than those of the others (log rank test, $\chi^2 = 14.42$, $P = 0.000$).

PATHOGENESIS OF ITCH

The exact pathophysiological mechanisms of CKD-associated pruritus still remain unexplained.

1-IMMUNE HYPOTHESIS MICROINFLAMMATION

- Immune Imbalanced Th1 and Th2 responses leading to higher levels of Th1cell lead to hypersecretion of IL-2

- Elevated levels of c-reactive protein
  Raised interleukin-6 concentrations
  (Kimmel *et al*. *2006)*.

- levels of albumin and ferritin were lower and higher respectively

In patients with severe pruritus in comparison to nonpruritic

Mettang T. Nephrol Dial Transplant. 2002;17(9):1558-63

1-IMMUNE HYPOTHESIS AND MICROINFLAMMATION

1- Tanning patients with ultra violet (UV) B light -when only half of the body was irradiated- led to relief of UP.

2- Thalidomide (suppresses TNF-a production and leads to a predominant differentiation of Th2 lymphocytes with suppression of interleukin-2(IL-2)-producing Th1 cells) is effective in the therapy of UP .

A similar effect can be observed with tacrolimus

3- After kidney transplantation patients almost never complain about UP

4- Patients receiving IL-2 fo the treatment of malignant disease frequently report tormenting pruritus .

Nephrol Dial Transplant (2002) 17: 1558–1563

Nephrology Dialysis Transplantation

Invited Comment

Uraemic pruritus—new perspectives and insights from recent trials

Thomas Mettang[1], Christiane Pauli-Magnus[2] and Dominik Mark Alscher[1]

Hemodialysis International 2005; 9: 180–186

Uremic pruritus: A review

Jocemir R. LUCON
Nephrology Division, Department of Medicine, Universidade Federal Fluminense

2- Opioid Receptors and Central nervous alterations

Origin

The terminal branching of afferent nonmyelinated C fibers are located in the lower epidermis or dermal epidermal junction

Receptors:

A dedicated pruritis receptor has not yet been identified.

Pathway:

These C fibers enter the spinal cord by the dorsal roots and ascend to the superior central nervous system via the contralateral spinothalamic tract.

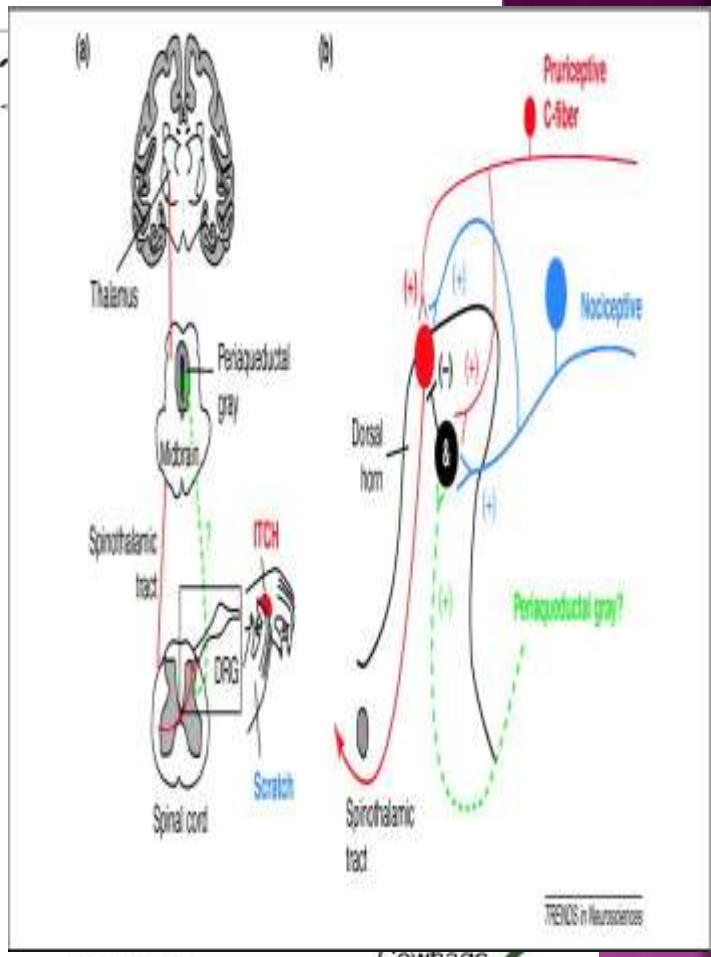
They reach the thalamus and hypothalamus by means of the reticular formation to the cerebral cortex.

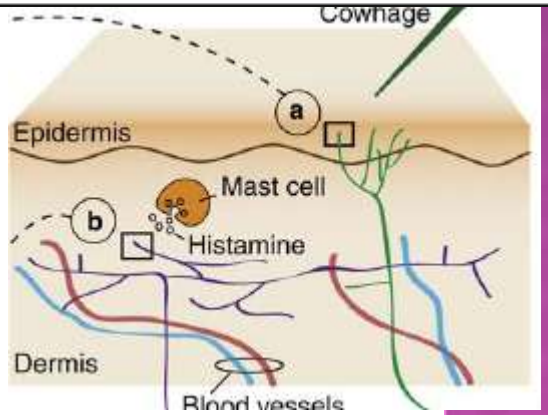
Center:

The anterior cingulate cortex,

The supplementar motor area

The inferior parietal lobe with a lefthemisphere predominance.





THE ‘OPIOID HYPOTHESIS’

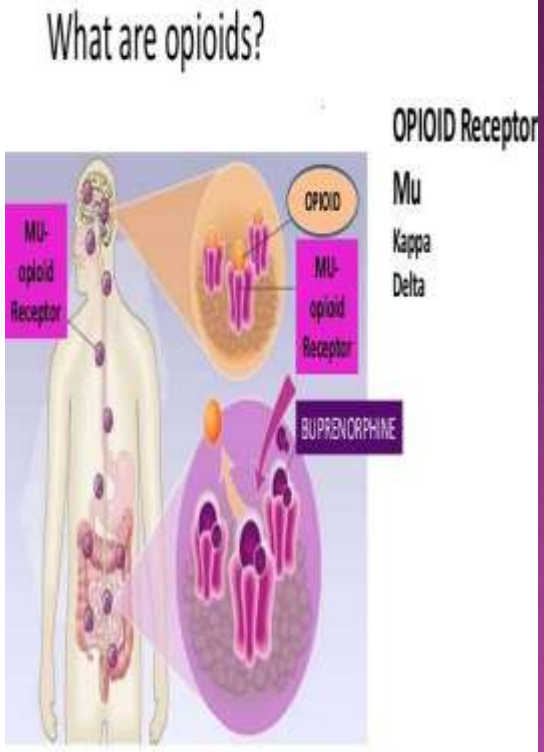
Changes in the opiodergic system might be involved in the pathophysiology of pruritus .

Lines of evidence:

First, several μ-receptor-agonistic drugs are known to induce pruritus.

Secondly, In animal studies cholestasis is associated with an increased opioidergic tone .

Thirdly, administration of opiate antagonists (k-receptors expressed by dermal cells and lymphocytes) was successful in the treatment of cholestatic pruritus.



Kumagai, H. et al. (2004)

OTHER CONTRIBUTING FACTORS

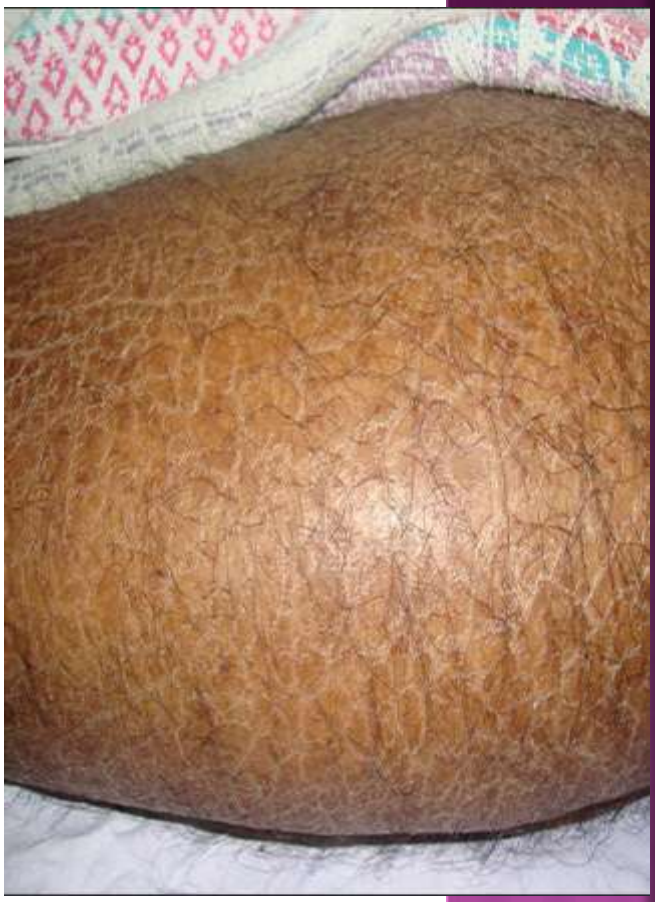
POTENTIAL CAUSES OF HEMODIALYSIS-RELATED PRURITUS

- Inadequate dialysis
- Accumulation of poorly dialysed compounds
- Hyperparathyroidism
- Hyperphosphatemia
- Increased calcium-phosphate deposition in the skin
- Xerosis
- Elevated serum magnesium and aluminum concentrations
- Sideropenic anemia
- Hypersensitivity to products used in the dialysis procedure
- Hepatitis C virus infection
- Peripheral neuropathy
- Inflammation

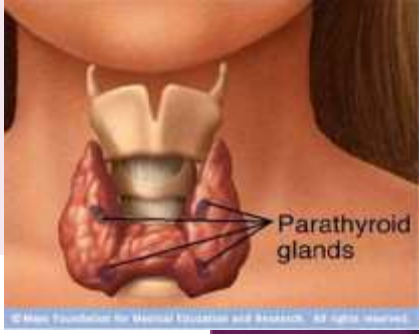
Xerosis

- Is the most frequent dermatological manifestation in patients undergoing dialysis therapy.
- Represent atrophy of sweat or sebaceous glands makes impairment of their function of external secretion.
- Sweat glands are known to be fibrosed and decreased in number in uremic skin.
- Aquaporin-3 (AQP-3), an integral membrane channel in keratinocytes .
- Facilitates the transport of glycerol from the circulation into the epidermis.
- Decreased AQP-3 expression in rat models of renal failure , could explain xerosis in CKD

Gong Het al . Nephrol Dial Transplant. 2003;18(12):2551-9



PARATHYROID GLAND



Is believed to be a possible pathogenetic factor.

persistent pruritus in patients with secondary Hyperparathyroidism improved after parathyroidectomy.

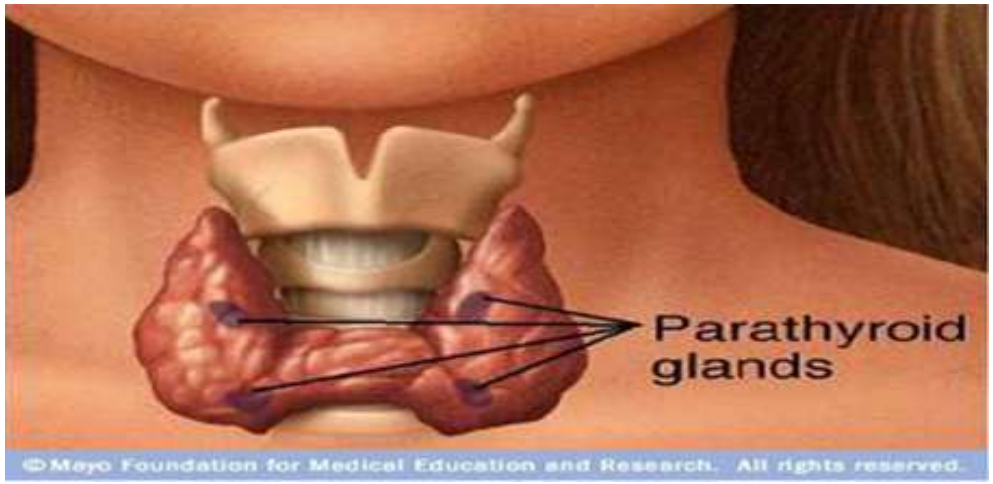
Can stimulate mast cells to release histamine and it can promote micro precipitation of calcium and magnesium salts in the skin.

Kleeman CR e tal ,. *Trans Assoc Am Physicians*. 1968, Massry SG, *N Engl J Med*. 1968

In contrast, parathormone did not elicit any cutaneous reaction upon intradermal application in humans and could not be detected in skin biopsies of affected patients.

Ståhle-Bäckdahl M, et al. *J Intern Med*. 1989.

WELTER EDE Q, ET AL .EVALUATING THE ASSOCIATION BETWEEN ALTERATIONS IN MINERAL METABOLISM AND PRURITUS IN HEMODIALYSIS PATIENTS. AN BRAS DERMATOL. 2011;86(1):31–6.



http://www.kidney-international.org mini review

Uremic pruritus

Thomas Mettang[1] and Andreas E. Kremer[2]

[1]Department of Nephrology, Deutsche Klinik für Diagnostik, Wiesbaden, Germany and [2]Department of Medicine 1, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany

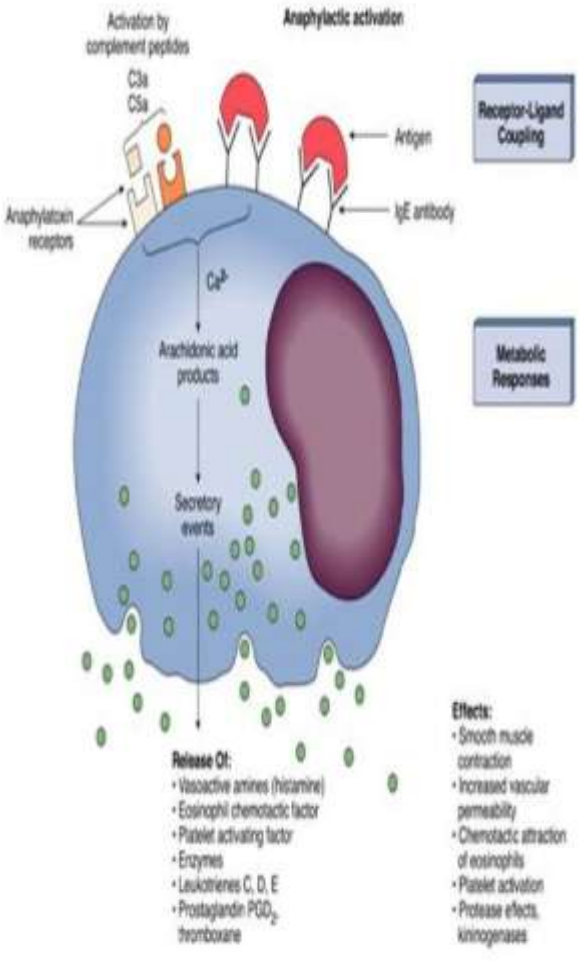
3- Role of Mast cells

- Contradictory data on the impact of histamine have been reported.
- Increased levels of histamine in patients with CKD-aP and suggested that accumulation of this classical pruritogen would have a key role.

Stockenhuber Fet al.. Clin Sci 1990; 79: 477–482.

- The absence of typical skin changes such as wheals
- Therapeutic failure of antihistamines in patients with CKD-aP
- challenge the concept of histamine as a major pruritogen.
- Increased levels of tryptase and substance released by mast cells were observed in patients with CKD-aP.

Weisshaar E. *Exp Dermatol*. 2004;13(5):298–304.



Acta Derm Venereol 2012; 92: 563–581

European Guideline on Chronic Pruritus

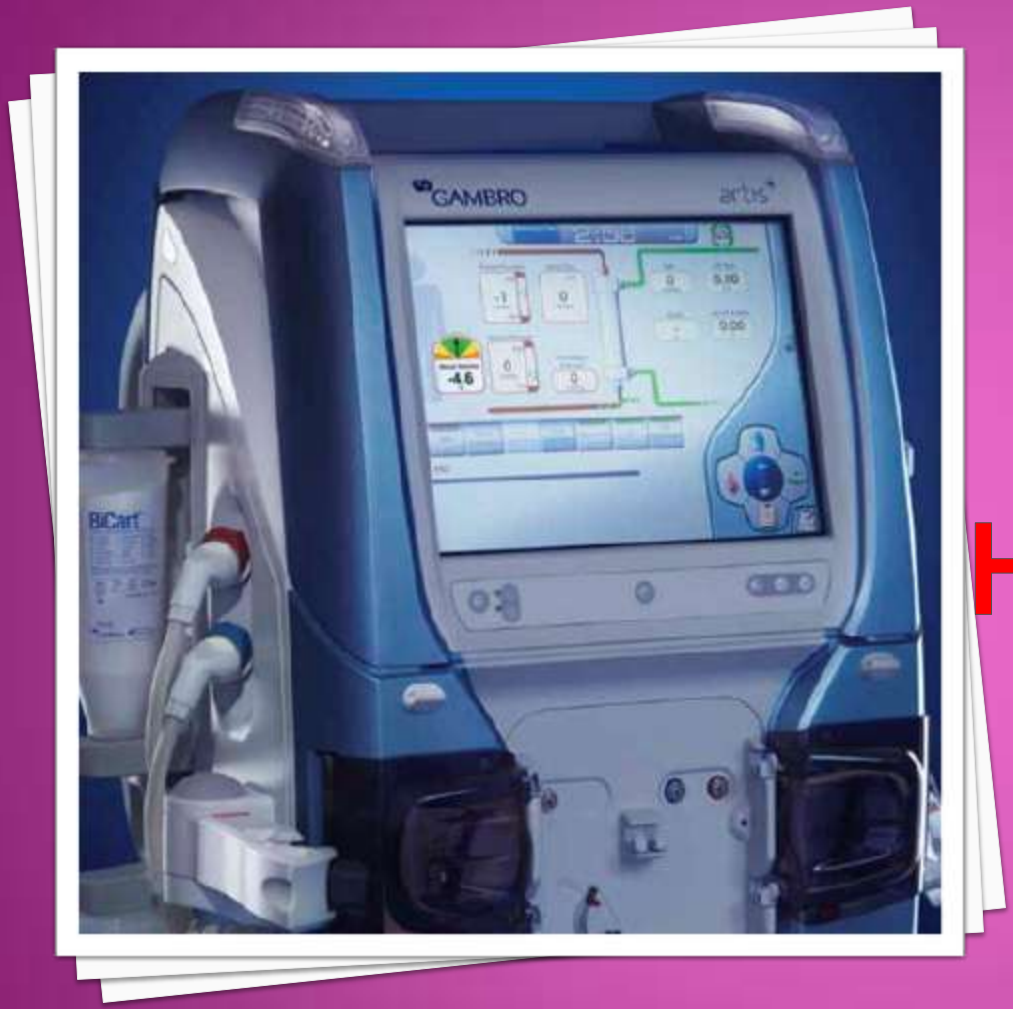
In cooperation with the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV)

Class of drug	Substance (examples)
ACE inhibitors	Captopril, enalapril, lisinopril
Antiarrhythmic agents	Amiodarone, disopyramide, flecainide
Antibiotics	Amoxicillin, ampicillin, cefotaxime, ceftriaxone, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, cotrimoxazole, erythromycin, gentamycin, metronidazole, minocycline, ofloxacin, penicillin, tetracycline
Antidepressants	Amitryptylin, citalopram, clomipramin, desipramine, doxepin, fluoxetine, fluvoxamine, imipramine, lithium, maprotiline, mirtazapine, nortriptyline, paroxetine, sertraline
Antidiabetic drugs	Glimepiride, metformin, tolbutamide
Antihypertensive drugs	Clonidine, doxazosin, hydralazine, methyldopa, minoxidil, prazosin, reserpine
Anticonvulsants	Carbamazepine, clonazepam, gabapentin, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid
Anti-inflammatory drugs	Acetylsalicylic acid, celecoxib, diclofenac, ibuprofen, indometacin, ketoprofen, naproxen, piroxicam
AT II antagonists	Irbesartan, telmisartan, valsartan
Beta blockers	Acebutolol, atenolol, bisoprolol, metoprolol, nadolol, pindolol, propranolol
Bronchodilators, mucolytic agents, respiratory stimulans	Aminophylline, doxapram, ipratropium bromide, salmeterol, terbutaline
Calcium antagonists	Amlodipine, diltiazem, felodipine, isradipine, nifedipine, nimodipine, nisoldipine, verapamil
Diuretics	Amiloride, furosemide, hydrochlorothiazide, spironolactone, triamterene
Hormones	Clomifene, danazol, oral contraceptives, estrogens, progesterone, steroids, testosterone and derivates, tamoxifen
Immunosuppressive drugs	Cyclophosphamide, cyclosporine, methotrexate, mycophenolatmofetil, tacrolimus (up to 36%), thalidomide
Antilipids	Clofibrate, fenofibrate, fluvastatin, lovastatin, pravastatin, simvastatin
Neuroleptics	Chlorpromazine, haloperidol, risperidone
Plasma expanders, blood supplying drugs	Hydroxyethyl starch, pentoxifylline
Tranquilizers	Alprazolam, chlordiazepoxide, lorazepam, oxazepam, prazepam
Uricostatics	Allopurinol, colchicine, probenecid, tiopronin

Drugs that may induce or maintain chronic pruritus (without a rash)

MANAGMENT OF CKD-ASSOCIATED PRURITUS

1. Haemodialysis-related therapy
   - Adequate haemodialysis
   - Correction of anaemia and treatment of secondary hyperparathyroidism and parathyroidectomy
   - Low calcium solutions
   - High flux membranes
2. Topical treatment
   - Antihistamines, glucocorticoids and moisturising creams
   - Capsaicin
   - Calcineurin inhibitors
   - Endocannabinoids
   - γ-linolenic acid
3. Physical therapies
   - Ultraviolet B (UVB) phototherapy
   - Acupuncture
4. Systemic treatment
   - μ-receptor antagonists (naloxone and naltrexone) and κ-receptor antagonists (nalfurafine)
   - Serotonin antagonists (ondasetrone and granisetrone)
   - SSRIs (paroxetine) and tricyclic antidepressants
   - Thalidomide
   - Ketotifen
   - Active charcoal
   - Antiepileptics (gabapentin)



(1) HEMODIALYSIS RELATED THERAPY

PLOS | ONE

Uremic Pruritus, Dialysis Adequacy, and Metabolic Profiles in Hemodialysis Patients: A Prospective 5-Year Cohort Study

Mei-Ju Ko , Hon-Yen Wu , Hung-Yuan Chen, Yen-Ling Chiu, Shih-Ping Hsu, Mei-Fen Pai, Ju-YehYang, Chun-Fu Lai, Hui-Min Lu, Shu-Chen Huang, Shao-Yu Yang, Su-Yin Wen, Hsien-Ching Chiu, Fu-Chang Hu, Yu-Sen Peng , Shiou-Hwa Jee

Published: August 6, 2013 • DOI: 10.1371/journal.pone.0071404

PLOS | ONE

Uremic Pruritus, Dialysis Adequacy, and Metabolic Profiles in Hemodialysis Patients: A Prospective 5-Year Cohort Study

Mei-Ju Ko, Hon-Yen Wu, Hung-Yuan Chen, Yen-Ling Chiu, Shih-Ping Hsu, Mei-Fen Pai, Ju-YehYang, Chun-Fu Lai, Hui-Min Lu, Shu-Chen Huang, Shao-Yu Yang, Su-Yin Wen, Hsien-Ching Chiu, Fu-Chang Hu, Yu-Sen Peng, Shiou-Hwa Jee

Published: August 6, 2013 • DOI: 10.1371/journal.pone.0071404

A prospective cohort study of patients with maintenance hemodialysis in the hemodialysis center of the Far Eastern Memorial Hospital had been conducted from February 2007 to July 2011. At the start of this period, a total of 374 patients were receiving transplantations, and 45 patients transferred to other hemodialysis centers. A total of 111 patients remained until the follow-up in July 2011 and completed the study. The study participants received 3.5–5.0 hours of hemodialysis three times a week using bicarbonate dialysate and reverse osmosis purified water, with the target dose of Kt/V (amount of dialysis delivered: K = clearance of urea, t = time on dialysis, V = estimated total body water) ≥1.4 to ensure the adequacy of solute clearance [17]. In 73% of participants, a high-flux polysulfone membrane was used as the dialyzer, while the remaining 27% used a low-flux synthetic membrane dialyzer.

Pruritus Assessment

The severity of pruritus measured by the visual analogue scale (VAS) from 0 to 10 (0 = no pruritus, 10 = intolerable pruritus) was reported from each participant at baseline and follow-up. The evaluation of the baseline VAS score for each participant was completed in February 2007. In July 2011, the participants were re-evaluated using the VAS score to assess the severity of pruritus.

This is the first prospective cohort study to investigate clinical parameters and metabolic profiles for uremic pruritus in hemodialysis patients using repeatedly measured data. In the study, we have demonstrated that the aggravation of pruritus was associated with lower Kt/V after adjusting for a variety of confounding factors. We've also shown that the patients with baseline Kt/V below 1.5 suffered from aggravation of pruritus intensity.

In addition, we have found that the use of a high-flux dialyzer was associated with alleviation of pruritus intensity. Compared with low-flux dialyzers, a high-flux dialyzer more efficiently removes middle molecules ranging in size from 1000 to 15,000 D and has been shown to be associated with the improvement of plasma lipolytic activities [36], as well as lower rates of amyloidosis and mortality [37], [38]. Our study results are consistent with previous studies in demonstrating that uremic patients with pruritus have higher blood levels of urea nitrogen and β_2-microglobulin than do patients without pruritus [4], [8]. Nonetheless, further studies are warranted to identify pruritogenic substances and potentially novel targets in order to help relieve uremic pruritus.

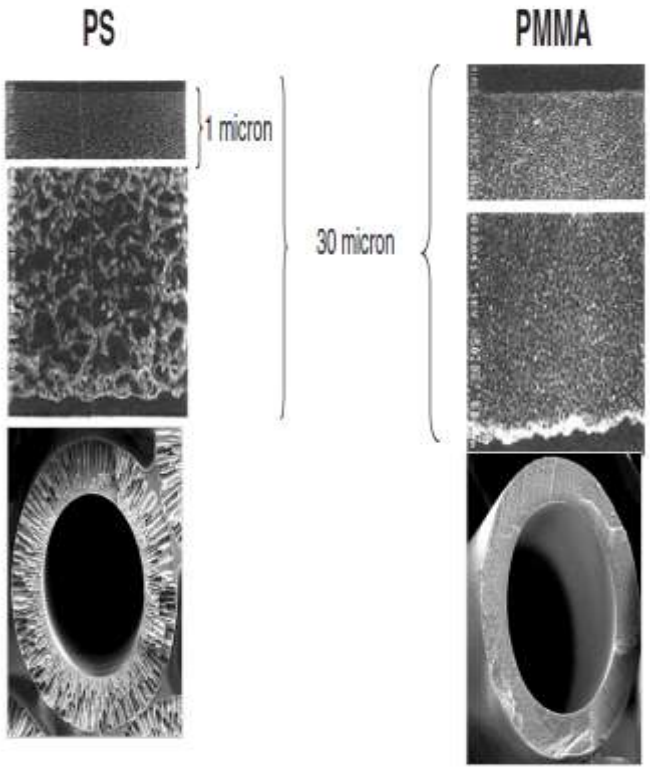
In conclusion, our study demonstrates that dialysis adequacy assessed by Kt/V is an independent predictor of pruritus intensity in patients with maintenance hemodialysis. Furthermore, hemodialysis with the target of Kt/V ≥1.5, as well as the use of high-flux dialyzer, may play a role in reducing the severity of uremic pruritus.

NDT Plus (2010) 3 [Suppl 1]: i8–i11
doi: 10.1093/ndtplus/sfq031

NDT PLUS
Nephrology Dialysis Transplantation

Review: the effect of polymethylmethacrylate dialysis membranes on uraemic pruritus

Filippo Aucella[1], Mimmo Vigilante[2] and Antonio Gesuete[1]



- Polymethylmethacrylate (PMMA)-dialysis membrane are based synthetic membranes with good solute permeability and a high degree of biocompatibility .
- Remove proteins by adsorption as well as permeation.
- Remove solutes of high MW (FLC)
- Adsorb solutes such as cytokines and some cationic compounds.

MODIFICATION OF DIALYSIS TECHNIQUES
DIALYSIS MEMBRANE

Artificial Organs
32(6):468–472, Blackwell Publishing, Inc.

Uremic Pruritus, Cytokines, and Polymethylmethacrylate Artificial Kidney

Hsin-Hung Lin, Yao-Lung Liu, Jiung-Hsiun Liu, Che-Yi Chou, Ya-Fei Yang, Huey-Liang Kuo, and Chiu-Ching Huang

Department of Medicine, Division of Nephrology, China Medical University Hospital, Taichung, Taiwan

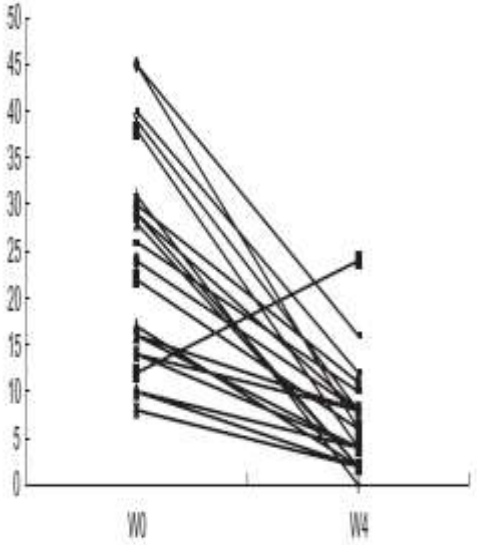


FIG. 1. The pruritus scores of the 24 patients before and after 4 weeks of PMMA AK use. W0, before the PMMA AK use; W4, after 4 weeks of PMMA AK use.

- **30 patients with severe CKD-ap**
- **Their dialyzers were changed to PMMA AK for 4 weeks.**
- **PMMA AK was effective in reducing the pruritus score**
- ***The effect of uremic pruritus relief* appeared after 1 week of PMMA AK use.**

MODIFICATION OF DIALYSIS TECHNIQUES

Disappearance of uraemic pruritus after lowering dialysate magnesium concentration

BMJ British Medical Journal

Restore nerve conduction velocity towards normal in patients receiving HD, and this could be the reason for the complete disappearance of pruritus .

Graf, H., et al. (1979)

Magnesium free dialysis for uraemic pruritus

Andrew J Carmichael, Fred Dickinson, Mary I McHugh, Anthony M Martin, Malcolm Farrow

Showed that a magnesium- free dialysis fluid corrected hypermagnesaemia, it failed to improve renal itch.

It was associated with an increased concentration of parathyroid hormone.

A potential of producing renal osteodystrophy in the long term.

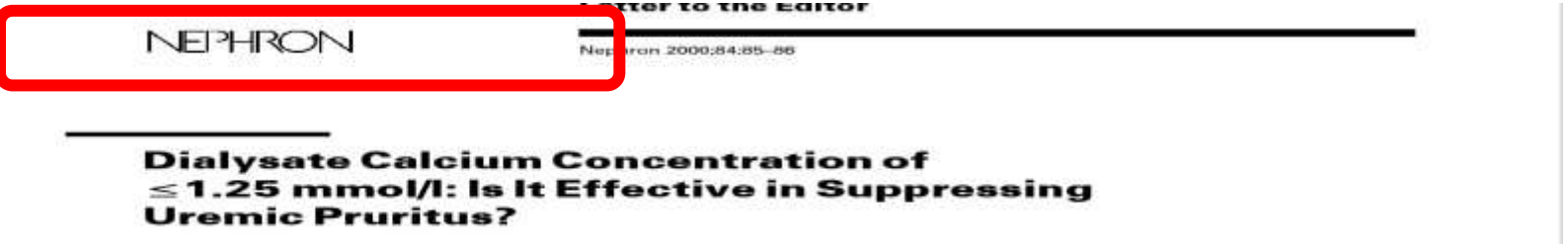
Carmichael, A.J., et al. (1988)

MODIFICATION OF DIALYSIS TECHNIQUES

LOWERING DIALYSATE CALCIUM

It has been postulated that calcium contributes to itching by influencing the degranulation of cutaneous mast cells

***Reduction in dialysis* calcium concentrations from 1.75 to 1.0 mmol/L was associated with a 41.421% ± 8.47% (*P < 0.05) relief* from itching in 4 HD patients,**



(2) TOPICAL TREATMENT

TOPICAL TREATMENT
A) EMOLLIENTS

- **There are no good comparative trials between various emollients for uremic pruritus.**
- **A high water content emollient rather than other agents is better .**
- **Daily topical treatment using rehydrating emollients should be regarded as baseline especially when a component of dry skin is found during clinical examination .**
- **Other topical applications performed are safflower oil, olive oil, primrose oil.**

Grade 1B

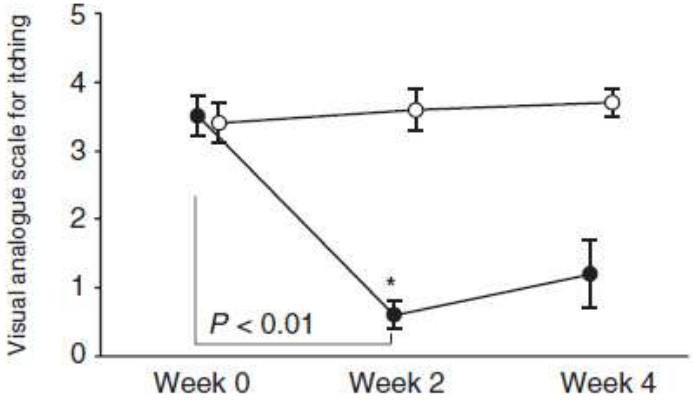
TOPICAL TREATMENT
A) EMOLLIENTS

Therapeutic Apheresis and Dialysis
8(5):419–422, Blackwell Publishing, Inc.

Effect of Skin Care With an Emollient Containing a High Water Content on Mild Uremic Pruritus

Kazuyoshi Okada and Keiichi Matsumoto

20 HD patients were divided into two groups; one group was treated with an aqueous gel containing 80% water .
The emollient was applied twice daily for 2 weeks



	Skin dryness			Skin scratching		
	Week 0	Week 2	Week 4	Week 0	Week 2	Week 4
Control group	1.1±0.1	1.2±0.1	1.3±0.3	1.1±0.2	1.2±0.2	1.2±0.2
Experimental group	1.1±0.1	0.1±0.1[b,d]	0.5±0.2	1.0±0.3	0.1±0.1[b,d]	0.2±0.1[b,d]

[a]$P < 0.05$ vs baseline value; [b]$P < 0.01$ vs baseline value; [c]$P < 0.05$ vs control group at same week; [d]$P < 0.01$ vs control group at same week.

The change of visual analog scale for itching in the two study groups.

Change of skin condition in the two study groups

TOPICAL TREATMENT
A) ANALGESICS

An alkaloid extract , Naturally-derived agent that may be helpful in reducing pruritus is capsaicin.

Mechanism:

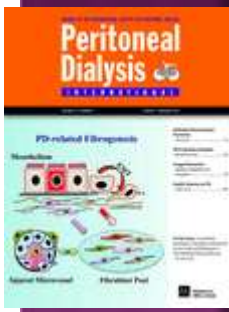
Capsaicin owes its potential antipruritic properties to desensitization of nociceptive nerve endings depleting the peripheral neurons of substance P .

However, the painful burning sensation associated with capsaicin use frequently leads to treatment withdrawal.

TOPICAL TREATMENT TACROLIMUS OINTMENTS

A preliminary study of three patients on peritoneal dialysis with severe CKD-aP.

Tacrolimus 0.03% ointment twice daily to the most affected areas for period of 7 days.



Strongly improved pruritus during treatment period , pruritus rose back to baseline values within days after end of treatment.

Pauli-Magnus Cet al. Perit Dial Int 2000;

A double blind, vehicle-controlled study conducted on 22 hemodialysis patients showed

No difference between tacrolimus and vehicle could be demonstrated

Duque MI, et al.. J Am Acad Dermatol 2005

Drawbacks:

black box warning has been issued against the prolonged use of topical tacrolimus because of an increased risk of skin malignancies demonstrated in animals.

Duque, M.I., et al . (2006) *Clinical Nephrol*

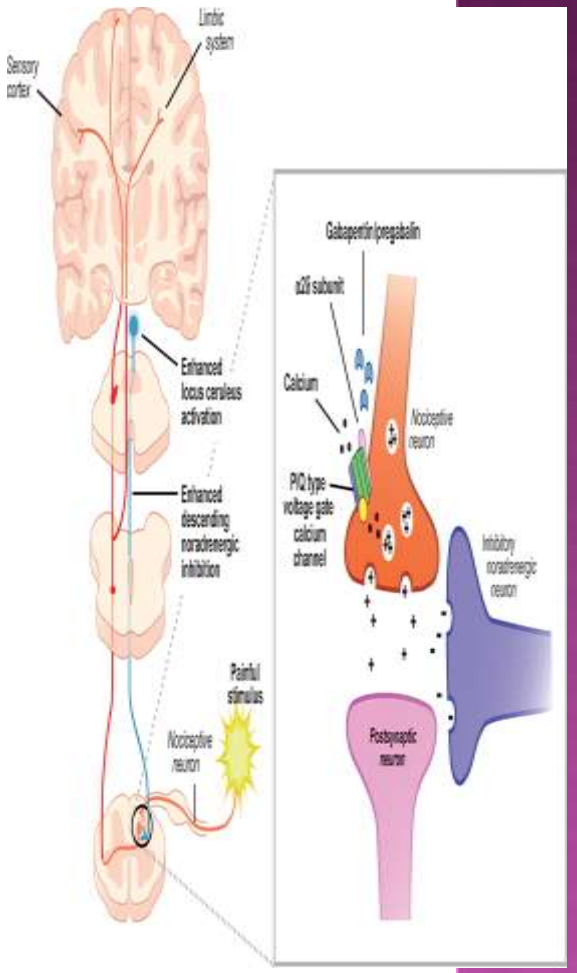
RESISTANT PRURITUS

Continued symptoms ➢ despite adequate dialysis, optimization of metabolic parameters, and the use of topical emollients and analgesics for approximately four weeks.

GABAPANTIN

SYSTEMIC TREATMENT
GABAPENTIN

- **An analogs of the major inhibitory neurotransmitter γ-aminobutyric acid (GABA).**
- **The mechanism of gabapentin in treating pruritus is not fully understood**
- **Centrally acting calcium-channel-blocker.**
- **Gabapentin has been studied for the treatment of several types of pruritus**



Naini AE,. Saudi J Kidney Dis Transplant 2007

SYSTEMIC TREATMENT GABAPENTIN

Nephrol Dial Transplant (2004) 19: 3137–3139
doi:10.1093/ndt/gfh496

Nephrology Dialysis Transplantation

Original Article

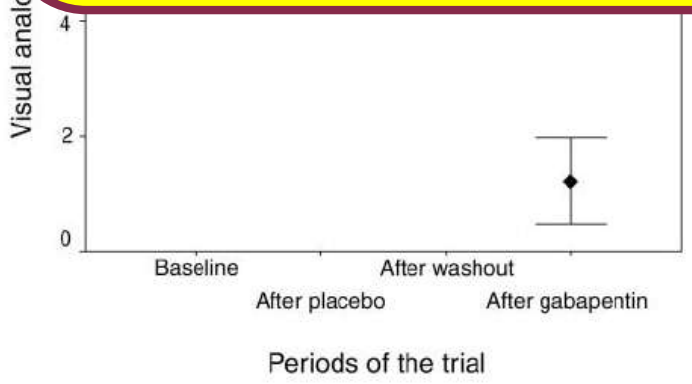
Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial

Ali Ihsan Gunal[1], Goksel Ozalp[1], Tahir Kurtulus Yoldas[2], Servin Yesil Gunal[3], Ercan Kirciman[1] and Huseyin Celiker[1]

[1]Department of Nephrology, [2]Department of Neurology and [3]Department of Biochemistry, Firat Univ

- **Gabapentin is completely dependent on renal elimination.**
- **A much longer half-life in subjects on HD (132 h Vs 5-7) compared with that in healthy subjects .**

Wong MO, Eldon MA, Keane WF, et al.. J Clin Pharmacol 1995;35:622-6



Changes in the pruritus scores before and after interventions.

- **was safe and highly effective in reducing pruritus.**
- **Itch intensity determined by a VAS dropped after 4** weeks of treatment.

SYSTEMIC TREATMENT
PREGABALIN

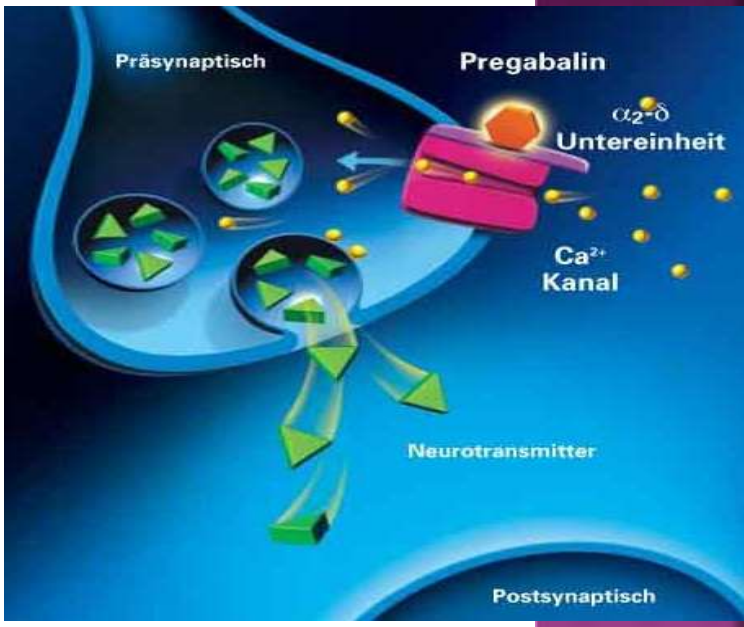
Its mechanism of action is similar to gabapentin, a central nervous system

1) The affinity of pregabalin to the 2-units of voltage-gated calcium

channels in CNS is six times higher compared with gabapentin .

(2) Decreases the secretion of neurotransmitters (substance P, norepinephrine and glutamate)

(Taylor *et al*. *2007)*



THE USE OF PREGABALIN IN THE TREATMENT OF URAEMIC PRURITUS IN HAEMODIALYSIS PATIENTS

Georgios Aperis, MD, PhD, Christos Paliouras, MD, Angelos Zervos, MD, Antonios Arvanitis, MD, Polichronis Alivanis, MD, PhD
Department of Nephrology, General Hospital of Rhodes, Rhodes 85100, Greece

180 Journal of Renal Care 2010

Sixteen haemodialysis patients suffering from uraemic pruritus.

Pregabalin 25 mg/day orally in the evening before sleep.

The severity of pruritus was tested before and one month after the initiation of pregabalin by using visual analog scale (VAS).

	Pre	Post	T	P value
Ht (%)	37.5 ± 5.9	36.6 ± 4.9	0.11	NS
Eos (mm^{-3})	459 ± 417.6	525 ± 332.2	0.12	NS
Ca (mg/dl)	9.4 ± 2.1	8.9 ± 1.5	0.19	NS
PO_4 (mg/dl)	5.5 ± 2.1	5.3 ± 2.3	0.06	NS
Ca x PO_4 (mg^2/dl^2)	50.9 ± 17.7	49.2 ± 14.4	0.07	NS
PTH (pg/ml)	281 ± 336	244 ± 221	0,09	NS
IgE IU/ml	37.3 ± 41.8	39.2 ± 31.6	0.03	NS
Kt/V	1.16 ± 0.2	1.13 ± 0.3	0.08	NS
VAS	7.44 ± 2.01	1.7 ± 1.31		<0.0003

(1)
ULTRAVIOLET RAYS (PHOTOTHERAPY)

ULTRAVIOLET IRRADIATION

Although exact mechanisms of UVB therapy in CKD-associated pruritus is unknown.

1- UVB induces apoptosis of dermal mast cells. (Suppression of histamine release from cutaneous mast cells)

Szepietowski JC,. Med Hypotheses 2002.

2-Reduces the release of neuropeptides such as substance P by decreasing epidermal nerve fibers.

Wallengren J, Sundler F.. Acta Derm Venereol 2004

3- Decreases the production pruritogenic IL-2.

4- Reduce cytokine production by lymphocytes

Zanolli M. Acad Dermatol 2003

Grade 2C

UVA (320-400 nm)

Reaches to the dermis and therefore can affect T lymphocytes, mast cells, and dermal dendritic cells

UVB (290-320 nm) :

limited penetration into the skin.

Affects epidermal keratinocytes and Langerhans' cells .

NB UVB (311nm)

is generally accepted to be less carcinogenic and less erythemogenic than BB UVB.

Rivard J, Lim HW. Ultraviolet phototherapy for prur

Dermatol Ther 2005; 18: 344-

ULTRAVIOLET IRRADIATION

17 patients

Treated thrice weekly with total body exposure to either UVA or UVB light.

UVB light resulted in resolution of pruritus in all cases.

UVA light was without any significant effect.

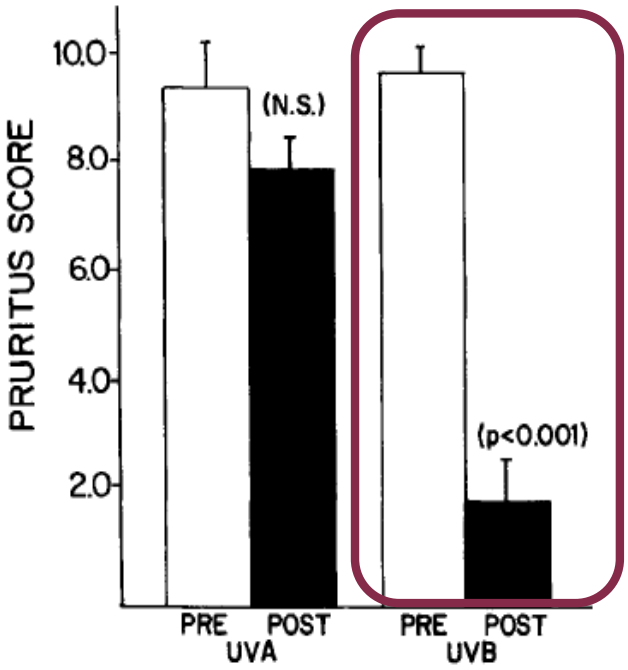


Fig 1. Effect of UVA and UVB phototherapy on pruritus, as measured by subjective rating on a scale of 1 to 10. Values are mean ± SEM.

1985

Uremic Pruritus: Skin Divalent Ion Content and Response to Ultraviolet Phototherapy

Jon D. Blachley, MD, D. Michael Blankenship, MD, Alan Menter, MD, Tom F. Parker III, MD, and James P. Knochel, MD

Identifying effective treatments for uremic pruritus

Jerry K. L. Tan, MD,[a] Herbert F. Haberman, MD,[b] and Andrew J. Coldman, PhD[c]
Vancouver, British Columbia, and Toronto, Ontario,

(J Am Acad Dermatol 1991;25:811-8.)

The risk for skin malignancies following UVB irradiation remains a matter of debate.

Thus, patients should be carefully evaluated before considering UVB therapy.

Ko MJ, et al Br J Dermatol 2011; 165: 633-639

					cm² UVA	
Trial duration	2 wk	4 wk	4 wk	4 wk	6 wk	6 wk
Follow-up	—	2-11 mo	—	8 wk	14 wk	6 wk

*Half-body UVB trial.
†One nondialyzed patient.

81%. Pooled data of the proportions of patients improving from the three whole-body UVB trials retained the significant effect ($p = 0.0001$; odds ratio 18.0, 95% confidence interval 4, 161; χ^2 test of homogeneity = 1.62, $p = 0.0001$). Adverse effects

Treatment of uremic pruritus with narrowband ultraviolet B phototherapy: An open pilot study

Simin Ada, MD,[a] Deniz Seçkin, MD,[a] İrem Budakoğlu, MD,[b] and Fatma Nurhan Özdemir, MD[c]
Ankara, Turkey

doi:10.1016/j.jaad.2004.12.052

Phototherapy was administered whole body surface 3 to the times a week for 6weeks.

In10 patients completed the 6-week study period.

Their pruritus intensity decreased by 70.8% in the VAS score.

In the follow-up period,

Recurrence:

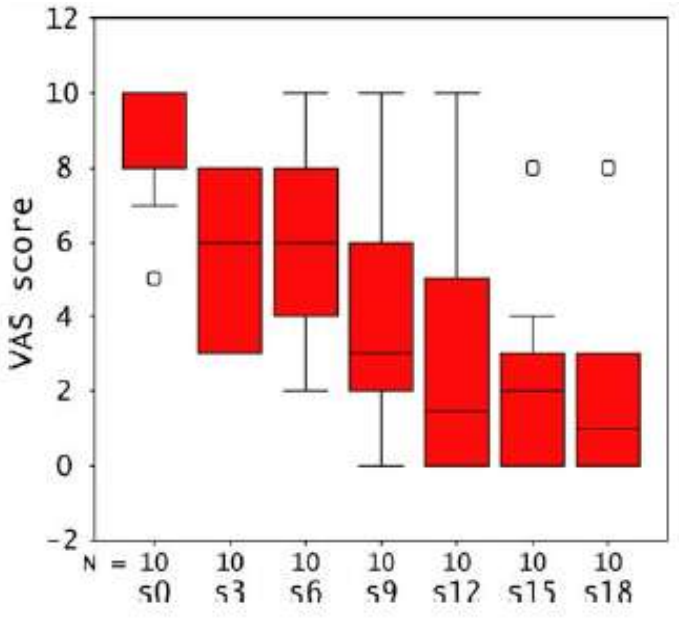
(57%) 4 patients pruritus recurred

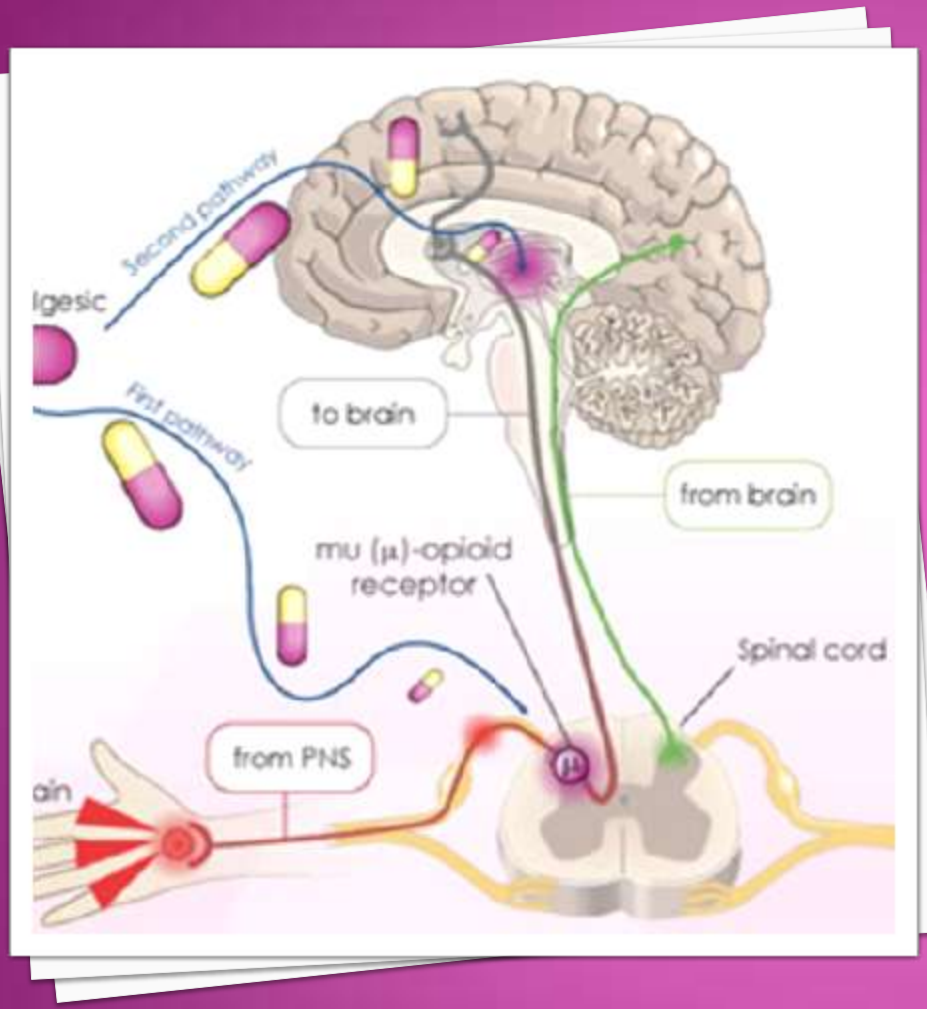
The mean time interval until recurrence was 2.5 months (range: 1-4 months).

Table I. Clinical characteristics and dialysis related data of the study patients

Median age, y (range)	44 (27-76)
Male/female sex	12/8
Skin phototype	II, 2 patients III, 4 patients IV, 14 patients
Duration of uremic pruritus (mo), mean ± SD	30 ± 41.7
Hemodialysis frequency/wk (n = 19)	3 times/wk
Hemodialysis solution, membrane type (n = 19)	Bicarbonated, hemophane
Hemodialysis duration (mo) (n = 19), mean ± SD	87.6 ± 64.8
Kt/V (n = 19), mean ± SD	1.07 ± 0.28

Kt/V, Fractional elimination of urea; an index of hemodialysis adequacy.



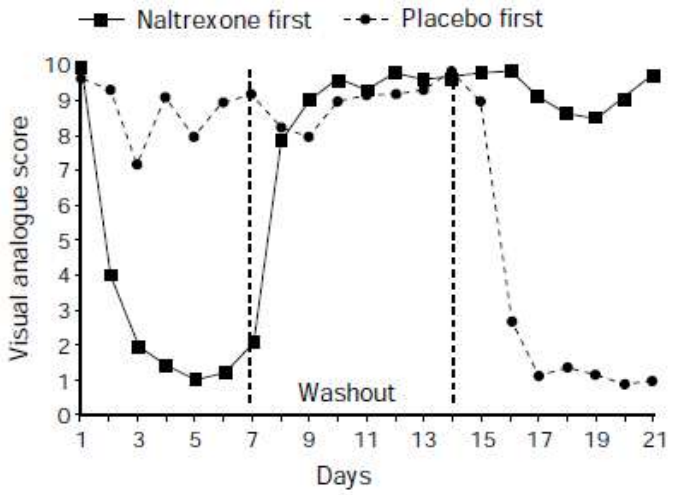


(2) OPIOID ANTGONIST AND AGONISTS

μ-OPIOID RECEPTOR ANTAGONISTS NALTREXONE.

A placebo-controlled, double-blind, crossover trial

Oral naltrexone for 1 week



Almost complete resolution of prur in 15 patients wit severe CKD-aP.

THE LANCET

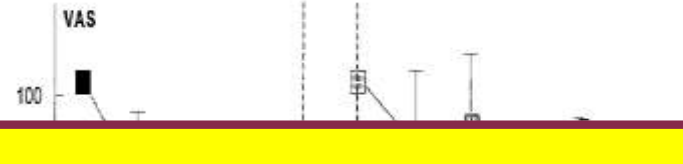
Randomised crossover trial of naltrexone in uraemic pruritus

Lancet 1996; **348:** 1552–54

Gary Peer, Shmuel Kivity, Orna Agami, Elizabeth Fireman, Donald Silverberg, Miriam Blum,

μ-OPIOID RECEPTOR ANTAGONISTS NALTREXONE.

A 4-week lasting placebo controlled, double-blind.



Results of the RCTs regarding NALTREXONE effects in uraemic pruritus were Contradictory .

•

J Am Soc Nephrol 11: 514–519, 2000

Naltrexone Does Not Relieve Uremic Pruritus: Results of a Randomized, Double-Blind, Placebo-Controlled Crossover Study

CHRISTIANE PAULI-MAGNUS,*† GERD MIKUS,† DOMINIK M. ALSCHER,*‡ TILLMANN KIRSCHNER,‡ WILFRIED NAGEL,§ NADJA GUGELER,† TEUT RISLER,‖ ELKE D. BERGER,‖ ULRICH KUHLMANN,* and THOMAS METTANG*‡

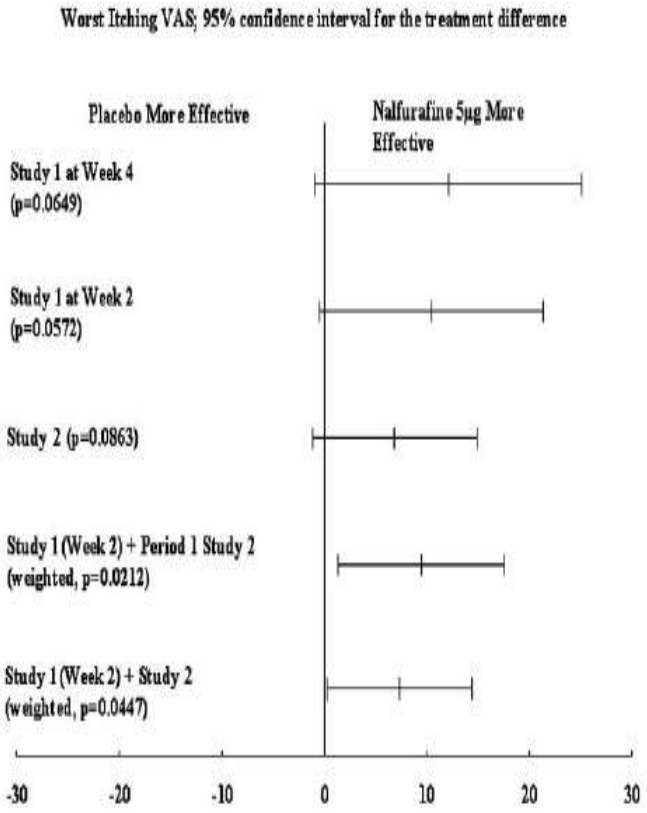
K-OPIOID RECEPTOR AGONISTS NALFURAFINE

A meta-analysis of two randomized doubleblind and placebo-controlled studies .

144 hemodialysis patients.

Nalfurafine was administered as a short infusion following hemodialysis three times weekly for a total period of 4 weeks

J Am Soc Nephrol 16: 3742–3747, 2005



Nalfurafine reduced the mean "worst itching" VAS significantly more than placebo

κ-Opioid System in Uremic Pruritus: Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Studies

Björn Wikström,* Ryszard Gellert,† Søren D. Ladefoged,‡ Yasuaki Danda,§ Masahiko Akai,§ Kaoru Ide,§ Midori Ogasawara,§ Yoshiharu Kawashima,§ Koki Ueno,§ Akio Mori,§ and

K-OPIOID RECEPTOR AGONISTS NALFURAFINE

A prospective, randomized, double-blind comparative study for 2 weeks

337 patients.

Compared the antipruritic effect of oral nalfurafine (2.5 and 5.0 μg) with a placebo .

The mean pruritus value as assessed by VAS decreased significantly to in weeks 2.

The most common ADR was insomnia (22.3%). Kumagai, H., et al., (2010) *Nephrology Dialysis Transplantation, **25, 1251-1257.***

An open-label study of 52-week.

211 HD patients with treatment-resistant itch.

The mean pruritus values as assessed by the VAS was 75.2 mm during the pre-observation period, which decreased significantly to 50.9 and 30.9 mm in weeks 52, indicating a long-lasting efficacy.

Frequent ADRs were insomnia (19.4%).

Kumagai, H.,., *et al. (2012). American Journal of Nephrology, **36*** 175-183

(3) ACUPUNCTUR

ACUPUNCTURE

Insertion of needles that are manipulated by the hands or by electrical stimulation into specific sites on the skin for therapeutic purposes.

To date, one of the most common hypotheses for the effects of acupuncture is the influence on the endogenous opioid system.

Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. Ann Intern Med 2002;136:374e383.

Experimental study suggested that the antipruritic effect of acupuncture might involve k-opioid receptor activation.

Zhao ZQ. Neural mechanism underlying acupuncture analgesia. Prog Neurobiol 2008;85: 3

ACUPUNCTURE

Electro-acupuncture or sham-electro- stimulation was applied to six patients on hemodialysis in a blinded manner .

Patients on acupuncture showed a significantly higher reduction in pruritus determined by a score than the sham-treated patients.

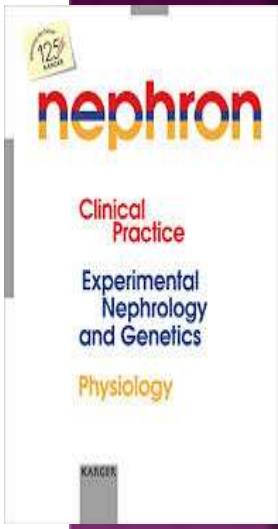
Duo LJ. Electrical needle therapy of uremic pruritus. Nephron 1987

40 patients with CKD-aP were treated with acupuncture either at the Quchi (LI11) acupoint or at a non-acupoint 2 cm lateral thrice weekly for 1 month.

Patients treated using the correct acupoint revealed a substantial reduction in pruritus.

Che-yi C, et al. Nephrol Dial Transplant 2005; 20: 912–915.

Acupuncture at least in experienced hands might be a useful tool in the treatment of CKD-aP.



Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2015, Article ID 208690, 5 pages
http://dx.doi.org/10.1155/2015/208690

Review Article

Efficacy of Acupuncture in Itch: A Systematic Review and Meta-Analysis of Clinical Randomized Controlled Trials

Chi Yu,[1] Pei Zhang,[1] Zheng-Tao Lv,[2] Jing-Jing Li,[1] Hong-Ping Li,[1] Cai-Hua Wu,[1] Fang Gao,[1] Xiao-Cui Yuan,[1] Jing Zhang,[1] Wei He,[3] Xiang-Hong Jing,[3] and Man Li[1]

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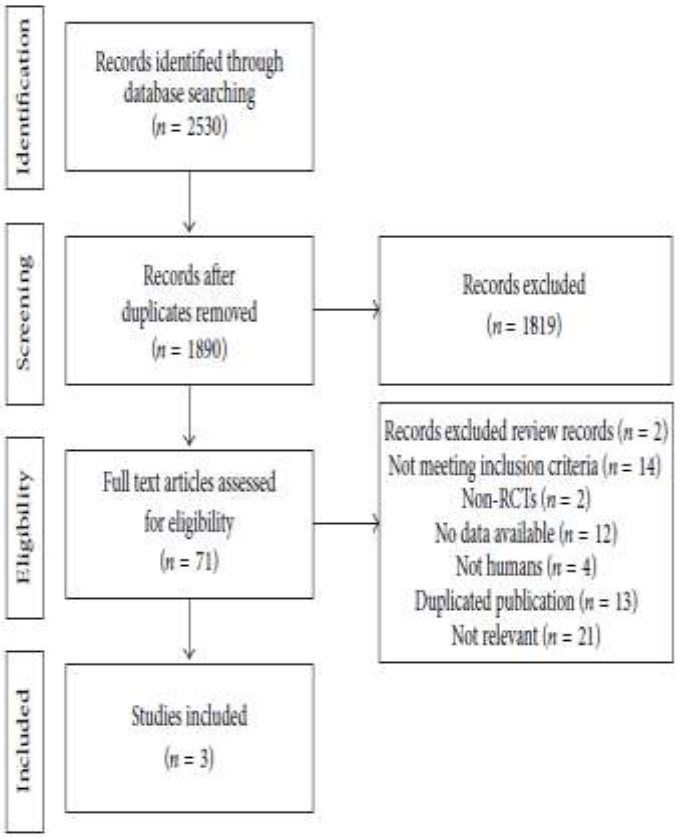

FIGURE 1

- A comprehensive literature search of **eight databases**
- **Randomized controlled trials** which compared acupuncture therapy and placebo
- **3 studies were published as full text between 2005 and 2011 from Taiwan and Germany.**

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
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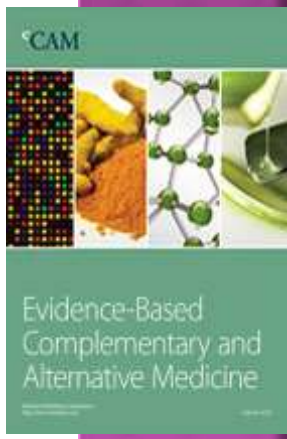
Acupuncture needs more studies on various ethnic samples to confirm our final conclusion.

Note: PA refers to placebo acupuncture and NT refers to no treatment.

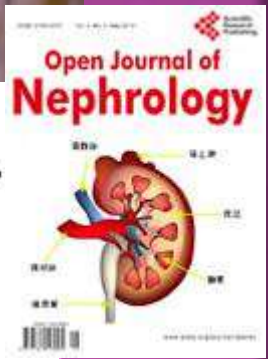


RUBDOWN WITH JAPANESE DRY TOWELS

- **Is a traditional Japanese alternative medicne.**
- **Subjects were naked or wore minimal clothing .**
- **Three sets of Japanese dry towels made with cotton.**
- **These towels were cleansed with water and then dried under sunlight.**
- **After drying, the subjects gently rubbed their whole body with these towels,**
- **This procedure was carried out in direct sunlight.**

Open Journal of Nephrology, 2015, 5, 1-18
Published Online March 2015 in SciRes. http://www.scirp.org/journal/ojneph
http://dx.doi.org/10.4236/ojneph.2015.51001

Scientific Research Publishing



Recent Advances in Treatment for Uremic Pruritus

Hiromichi Suzuki[1*], Hiroshi Omata[2], Hiroo Kumagai[3]

RUBDOWN WITH JAPANESE DRY TOWELS

1-Eliminates the bacterial flora on the surface of the skin and strengthen the barrier function of the skin.

2-Prevent intrusion of c-fiber from the dermis into the epidermis which is one of the causes of itch .

3- Activates natural killer cells, which may be attributed to the effect of certain mediators released from the T lymphocytes or the stimulated effect on the sympathetic nerves.

Open Journal of Nephrology, 2015, 5, 1-13
Published Online March 2015 in SciRes. http://www.scirp.org/journal/ojneph
http://dx.doi.org/10.4236/ojneph.2015.51001

Scientific Research Publishing

Recent Advances in Treatment for Uremic Pruritus

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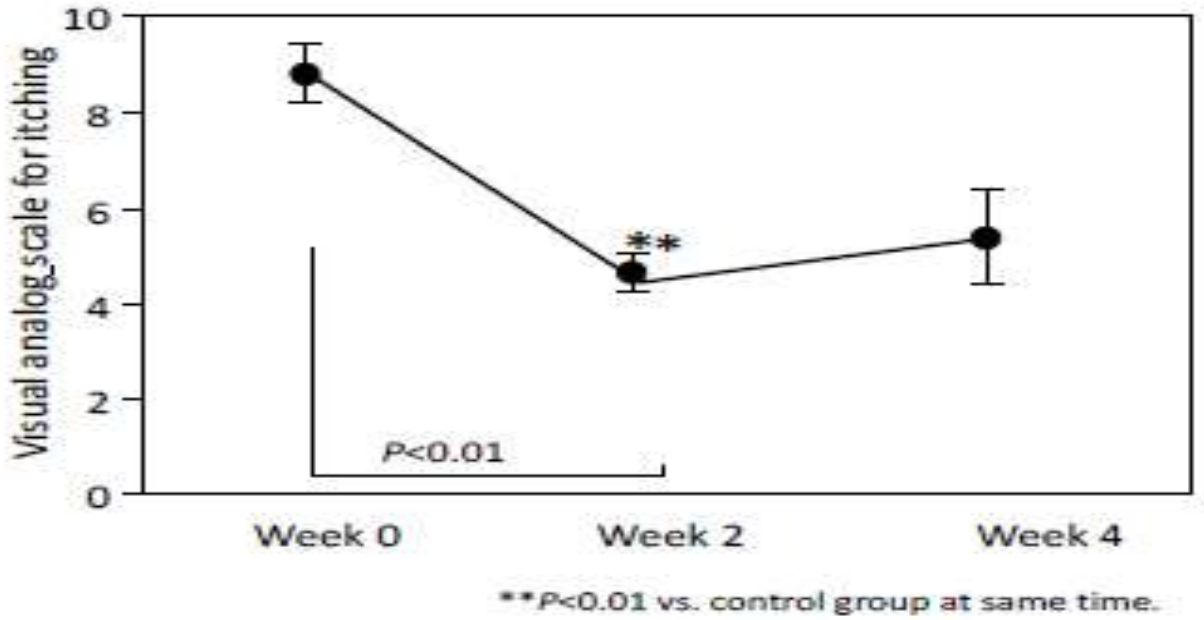
RUBDOWN WITH JAPANESE DRY TOWELS



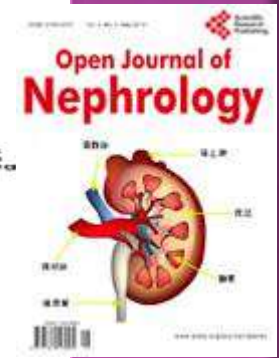
**P<0.01 vs. control group at same time.

Manipulation by rubdown with Japanese dry towels produced a marked reduction in pruritus

Open Journal of Nephrology, 2015, 5, 1-13
Published Online March 2015 in SciRes. http://www.scirp.org/journal/ojneph

Recent Advances in Treatment for Uremic Pruritus

Hiromichi Suzuki[1*], Hiroshi Omata[2], Hiroo Kumagai[3]



OTHERS

ORAL CHARCOAL

Act by binding putative pruritogens in the intestinal lumen

A crossover double-blind placebo-controlled study.

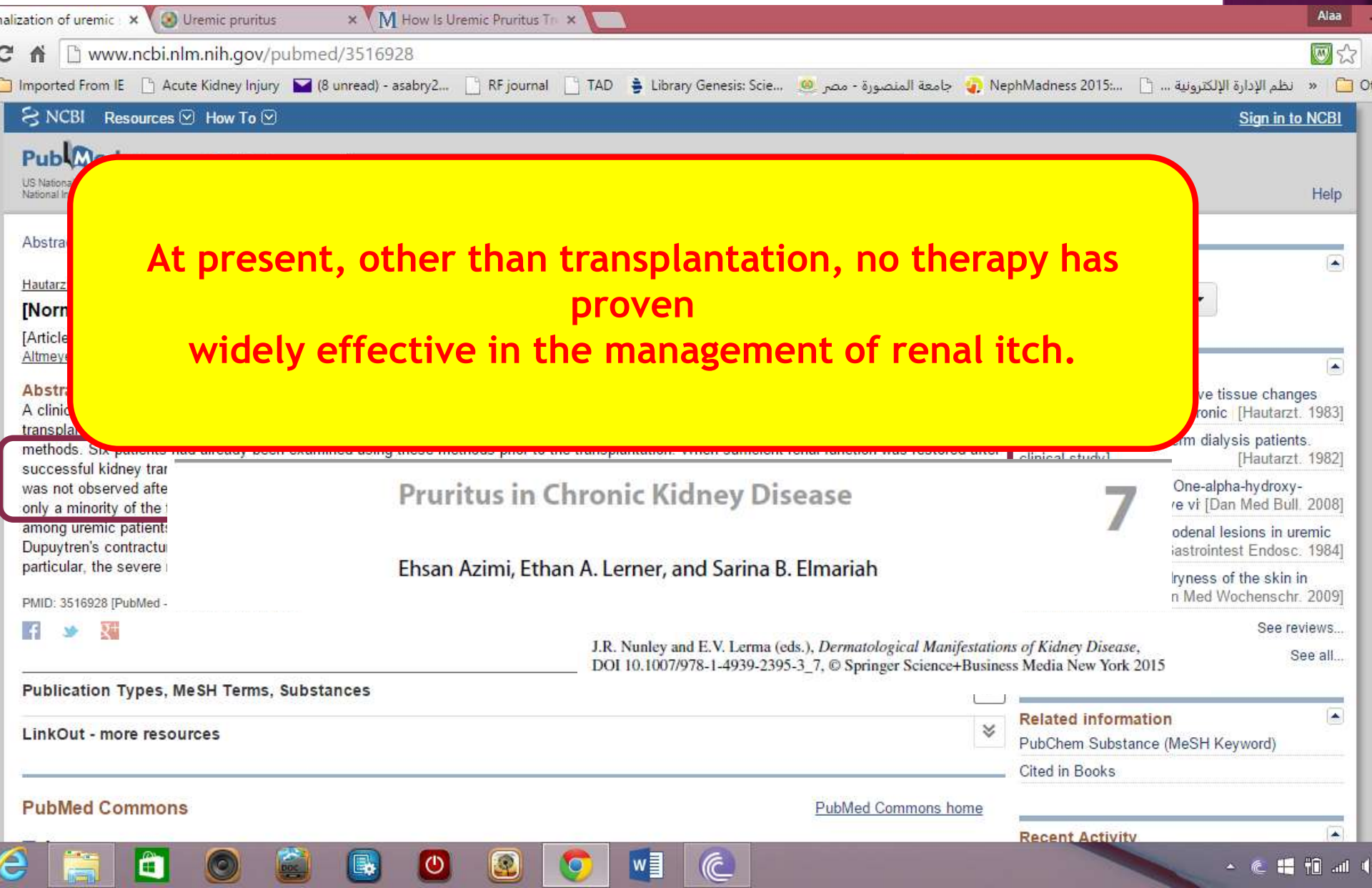
Twenty patients were enrolled and treated with 6 g/day for eight weeks.

Statistical significance in favor of treatment was only found in Phase 1 of the study using one-tailed statistics.

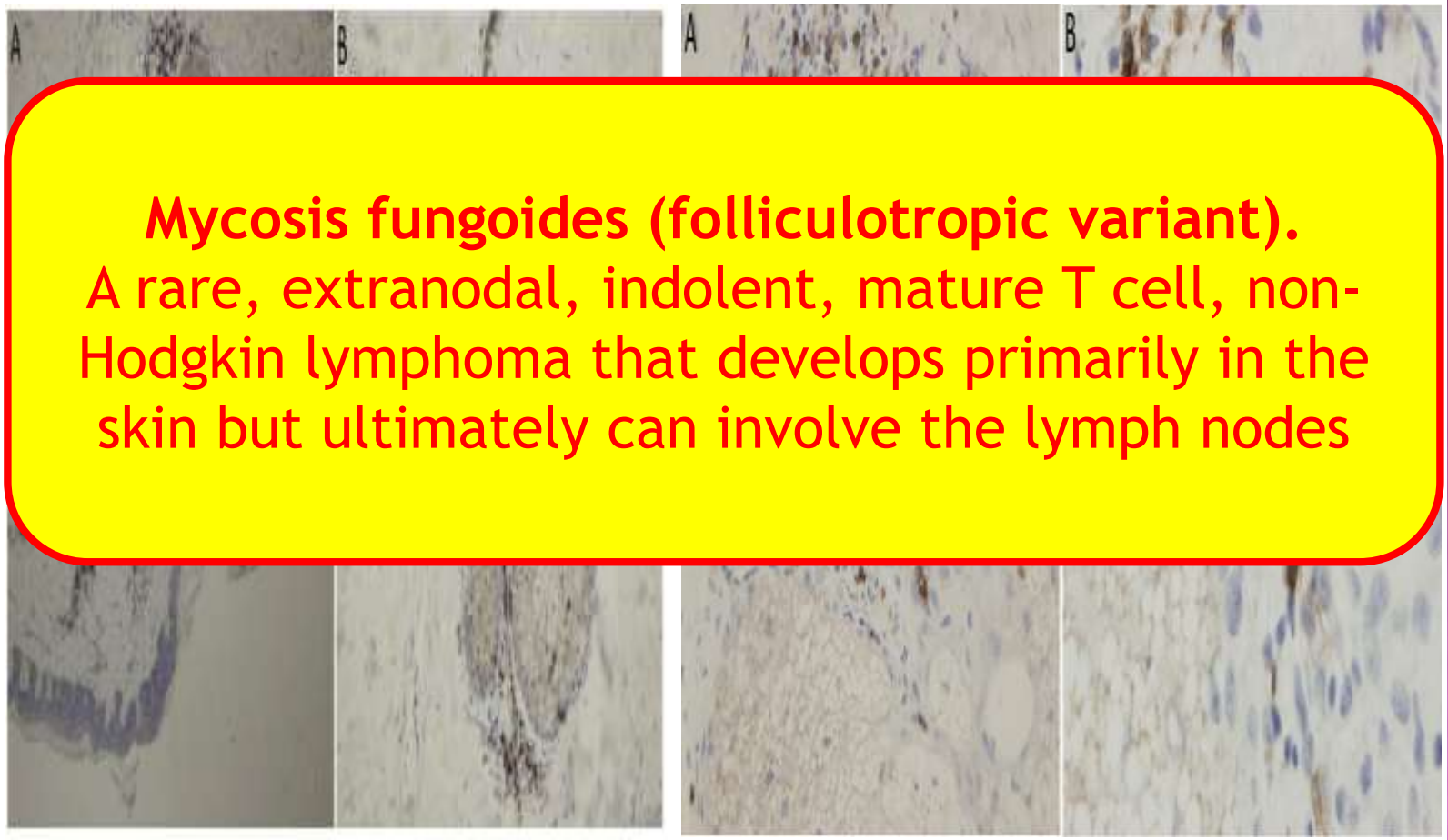
Cholestyramine, presumably acting in a similar way, was found to improve pruritus in a double-blind, placebo-controlled trial with 10 patients. Treated patients received 5 g twice a day for four weeks.

Pederson JA, et al. Relief of idiopathic generalized pruritus in dialysis patient treated with activated oral charcoal. Ann Intern Med 1980

KIDNEY TRANSPLANTATION



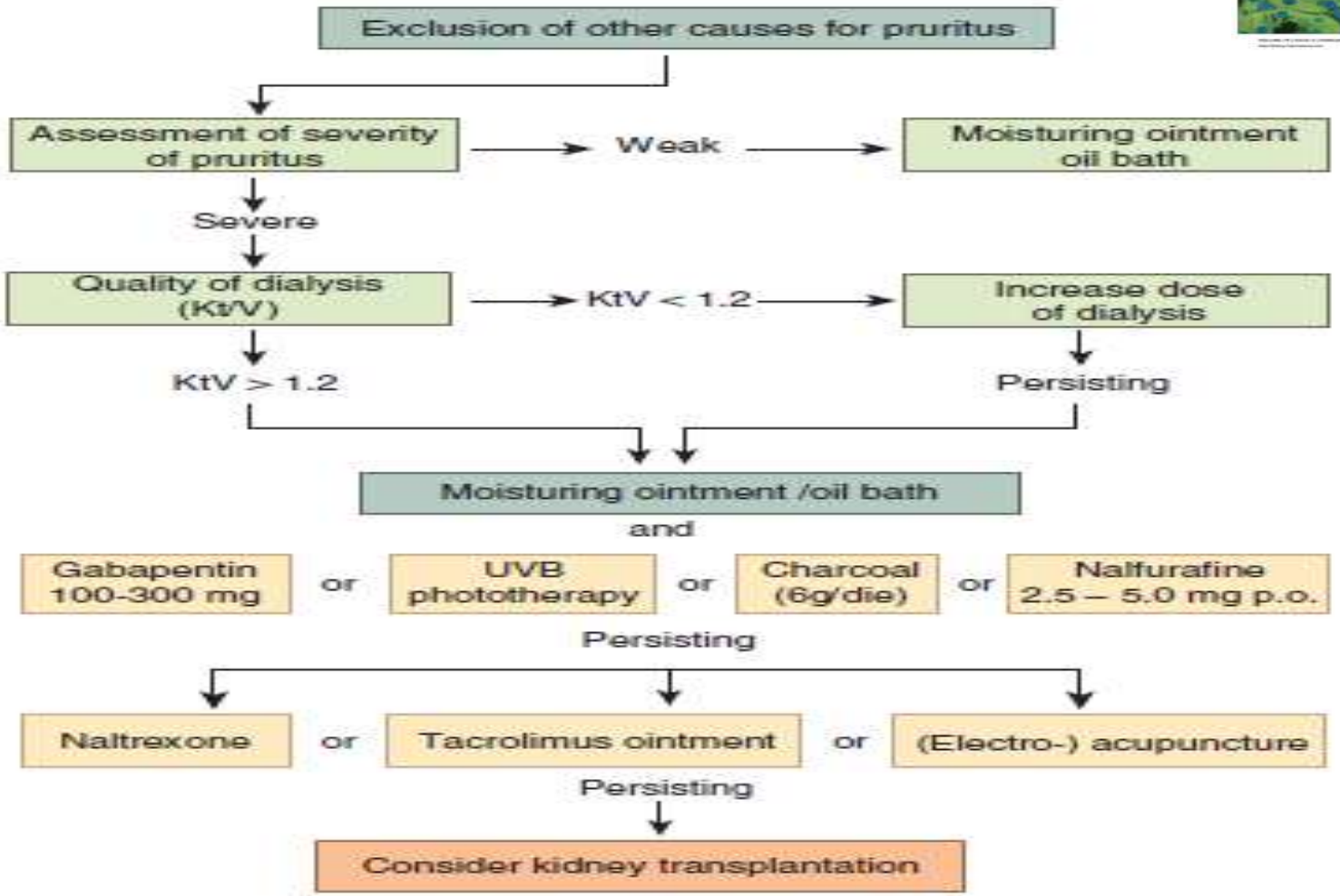
OUR CASE



Mycosis fungoides (folliculotropic variant).
A rare, extranodal, indolent, mature T cell, non-Hodgkin lymphoma that develops primarily in the skin but ultimately can involve the lymph nodes

Skin biopsy specimen shows epidermis without overt changes. The skin adnexa (hair follicle and sebaceous gland) show periadnexal infiltration with T lymphocytes (predominantly CD3+),Immunohistochemistry anti-CD3 stain .

THERAPEUTIC ALGORITHM IN (CKD-AP



http://www.kidney-international.org

mini review

Uremic pruritus

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CONCLUSION

CONCLUSION

- (CKD-aP) remains a frequent and compromising symptom in patients with advanced or end-stage renal disease .
- strongly reducing the patient's quality of life.
- The pathogenesis of CKD-aP remains obscure.
- Newer hypotheses are focusing on opioid-receptor derangements and microinflammation as possible causes of CKD-aP, although until now this could not be proven.

CONCLUSION

- Before making the diagnosis of uremic pruritus, other causes of pruritus must be ruled out.
- Treatment of CKD-aP remains frustrating and continues to present a significant therapeutic challenge.
- In desperate cases patients principally eligible for a kidney transplant may be switched to ‘high urgency’ status, which will decrease their waiting time.


Thank You!
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Takk skal
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